

Pulmonary Vasodilator Response to Adenosine Triphosphate-Sensitive Potassium Channel Activation Is Attenuated during Desflurane but Preserved during Sevoflurane Anesthesia Compared with the Conscious State

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Background: The objective of this study was to investigate the effects of sevoflurane and desflurane anesthesia on the pulmonary vasodilator response to the adenosine triphosphate-sensitive potassium channel agonist, lemakalim, compared with the response measured in the conscious state. In addition, the authors assessed the extent to which sympathetic α_1 -adrenoreceptor inhibition and cyclooxygenase pathway inhibition modulate the vasodilator response to lemakalim.

Methods: Twenty-four conditioned male mongrel dogs were chronically instrumented to measure the left pulmonary vascular pressure-flow relationship. After precontraction with the thromboxane analogue, U46619, dose-response relationships to lemakalim were assessed on separate days in the conscious state and during sevoflurane ($\approx 3.5\%$ end-tidal) and desflurane ($\approx 10.5\%$ end-tidal) anesthesia (~ 1.5 minimum alveolar concentration for each anesthetic agent). The effects of sympathetic α_1 -adrenoreceptor inhibition (prazosin) and cyclooxygenase inhibition (indomethacin) on the pulmonary vasodilator response to lemakalim also were assessed in the conscious and desflurane-anesthetized states.

Results: Neither sevoflurane nor desflurane had a net effect on the baseline left pulmonary vascular pressure-flow relationship compared with the conscious state. The magnitude of the pulmonary vasodilator response to lemakalim was

preserved during sevoflurane anesthesia but was attenuated ($P < 0.05$) during desflurane anesthesia compared with the conscious state. The attenuated lemakalim-induced vasodilator response during desflurane anesthesia was partially reversed ($P < 0.05$) by pretreatment with prazosin but not indomethacin.

Conclusion: These results indicate that adenosine triphosphate-sensitive potassium channel-mediated pulmonary vasodilation is preserved during sevoflurane anesthesia but is attenuated during desflurane anesthesia. The attenuated response to adenosine triphosphate-sensitive potassium channel activation during desflurane anesthesia is partially mediated by reflex sympathetic α_1 -adrenoreceptor vasoconstriction. (Key words: Circulation; indomethacin; lemakalim; prazosin; pressure-flow relationship.)

ADENOSINE triphosphate (ATP)-sensitive potassium (K^+_{ATP}) channels are important in the regulation of pulmonary vascular smooth muscle tone.¹ Activation of K^+_{ATP} channels results in membrane hyperpolarization and pulmonary vasodilation.^{2,3} We recently demonstrated that the pulmonary vasodilator response to K^+_{ATP} channel activation is attenuated during halothane and enflurane anesthesia compared with the response measured in the conscious state.⁴ The effects of the two new volatile anesthetic agents, sevoflurane and desflurane, on K^+_{ATP} channel-mediated pulmonary vasodilation have not been elucidated, however. This information is important because of the extensive clinical and investigational use of sevoflurane and desflurane, which provide rapid induction of anesthesia, easily controlled anesthetic depth, and fast emergence consistent with low blood gas and tissue partition coefficients.^{5,6}

Our objective was to test the hypothesis that sevoflurane and desflurane anesthesia would attenuate the pulmonary vasodilator response to the K^+_{ATP} channel agonist, lemakalim (BRL38227; a gift from SmithKline Beecham, Herts, UK), compared with the response mea-

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sured in the conscious state. Because we observed that the pulmonary vasodilator response to lemakalim was preserved during sevoflurane but attenuated during desflurane anesthesia, we also investigated the roles of reflex sympathetic α_1 -adrenoreceptor activation and cyclooxygenase metabolites in mediating the effect of desflurane on lemakalim-induced pulmonary vasodilation.

Materials and Methods

All surgical procedures and experimental protocols were approved by the Institutional Animal Care and Use Committee at The Cleveland Clinic Foundation.

Surgery for Chronic Instrumentation

Twenty-four conditioned male mongrel dogs (27 ± 1 kg) were premedicated with morphine sulfate (10 mg intramuscularly) and anesthetized with pentobarbital sodium (20 mg/kg intravenously) and fentanyl citrate (15 μ g/kg). After tracheal intubation, the lungs were mechanically ventilated. Anesthesia was maintained with halothane ($\approx 1.2\%$ end-tidal). With the use of sterile surgical technique, a left lateral thoracotomy was performed *via* the fifth intercostal space. The pericardium was incised ventral to the phrenic nerve. Heparin-filled Tygon catheters (1.02 mm ID; Norton, Akron, OH) were inserted into the descending thoracic aorta, left and right atria, and main pulmonary artery and were secured with purse-string sutures. After careful dissection and isolation, a hydraulic occluder (18 mm ID; In Vivo Metric, Healdsburg, CA) was positioned loosely around the right main pulmonary artery, and an electromagnetic flow probe (10 mm ID; Zepeda, Seattle, WA) was placed around the left main pulmonary artery. After loose apposition of the pericardial edges, the free ends of the catheters, occluder, and flow probe were threaded through the chest wall and tunneled subcutaneously to a final position between the scapulae. A chest tube placed in the left thorax before closure was removed 1 day after surgery. Morphine sulfate (10 mg) was administered intramuscularly after surgery for pain as required. Ampicillin (1 g), cefazolin (1 g), and gentamicin (80 mg) were administered intravenously during surgery and on a daily basis for 10 days after surgery. The dogs were allowed to recover for ≥ 2 weeks before experimentation.

Experimental Measurements

Vascular pressures were measured by attaching the fluid-filled catheters to strain-gauge manometers (Iso-

tec®; Quest Medical, Allen, TX), and were referenced to atmospheric pressure with the transducers positioned at midchest at the level of the spine. Heart rate was calculated from the phasic systemic arterial pressure (SAP) trace. Left pulmonary blood flow (LQ) was measured by connecting the flow probe to an electromagnetic flowmeter (SWF-5RD; Zepeda). The flow probe was calibrated *in vivo* on a weekly basis *via* the thermal dilution technique. This was achieved by acutely inserting a 7-French balloon-tipped thermal dilution catheter into the pulmonary artery through a percutaneous jugular puncture after topical anesthesia (lidocaine spray). The catheter was positioned 2–3 cm beyond the pulmonic valve. The implanted perivascular hydraulic occluder was then inflated to occlude the right main pulmonary artery completely, which directed total pulmonary blood flow through the left pulmonary artery (and flow probe). Left pulmonary blood flow was then measured by thermal dilution (HEMOPRO₂; Spectramed, Oxnard, CA) with multiple 10-ml sterile injectates of 5% dextrose in water. Values for LQ were referenced to body weight ($\text{ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$). The aortic and pulmonary artery catheters were used to obtain blood samples to measure systemic arterial and mixed venous blood gases, respectively. Systemic arterial and mixed venous pH, carbon dioxide tension, and oxygen tension were measured with an ABL-600 (Radiometer, Copenhagen, Denmark). Oxyhemoglobin saturation was measured with a Hemoximeter OSM-3 (Radiometer).

Experimental Protocols

All experiments were performed with each healthy, chronically instrumented dog lying on its right side in a quiet laboratory environment. Conscious dogs were not sedated. Left pulmonary vascular pressure-flow (LPQ) plots were used to assess the effects of the various pharmacologic interventions on the pulmonary circulation. LPQ plots were constructed by continuously measuring the pulmonary vascular pressure gradient (pulmonary arterial pressure [PAP]–left atrial pressure [LAP]) and LQ during gradual (≈ 1 min) inflation of the hydraulic occluder implanted around the right main pulmonary artery. This technique to measure the LPQ relationship is highly reproducible and has little or no effect on systemic hemodynamics, blood gases, or the zonal condition of the lung.⁷

Protocol 1: Effect of Sevoflurane Anesthesia on the Pulmonary Vascular Response to Lemakalim.

We investigated the effect of sevoflurane anesthesia on the pulmonary vascular response to cumulative doses of the K^+_{ATP} channel agonist, lemakalim, after precontraction with the thromboxane analogue 9,11-dideoxy-11 α ,9 α -epoxymethano-prostaglandin $F_{2\alpha}$ (U46619 [a gift from Cayman Chemical, Ann Arbor, MI]). A baseline LPQ plot was first obtained in each conscious dog ($n = 6$). U46619 was then administered ($0.15 \pm 0.02 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ intravenously) to precontract the pulmonary circulation before the administration of lemakalim. Plots of LPQ were obtained during precontraction with U46619 alone and then again with each dose of lemakalim (0.1, 0.5, 1.0, and $5.0 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ intravenously) during its cumulative administration (≈ 15 min at each dose) while the infusion of U46619 was continued. We previously have verified that pulmonary vasoconstriction induced by U46619 is stable during the time course of this protocol.⁸ On a different day, this protocol was repeated in the same six dogs during sevoflurane anesthesia. Anesthesia with sevoflurane was induced by mask and was supplemented with a subanesthetic dose of thiopental sodium (3 mg/kg intravenously) to minimize excitatory behavior. The trachea was intubated (with a 9 mm ID tube), and ventilation was controlled with a respirator with zero end-expiratory pressure. Muscle relaxants were not used in this study. Immediately after intubation, sevoflurane was delivered *via* a vaporizer (Sevotec 3; Ohmeda, Austell, GA) with a fresh gas flow of $100 \text{ ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$. Tidal volume was fixed at 15 ml/kg. Systemic arterial blood gas values were matched to values measured in the conscious state by adjusting the respiratory rate to 10–20 breaths/min and by administering supplemental oxygen (fractional inspired oxygen tension = 0.26). End-tidal carbon dioxide tension and concentration of sevoflurane were monitored continuously at the adapter end of the endotracheal tube (Solar 7000; Marquette Electronics, Milwaukee, WI). After induction, sevoflurane was allowed to equilibrate for ≥ 1 h to achieve steady-state conditions. At this time, end-tidal concentrations of sevoflurane were 3.3–3.8% (minimum alveolar concentration, 1.4–1.6%).⁹ During sevoflurane anesthesia, the dose of U46619 ($0.12 \pm 0.01 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ intravenously) was titrated to achieve the same degree of precontraction induced in the conscious state. The titration procedure involved administering incremental doses of U46619 and generating LPQ plots until a dose was found that caused the same increase in PAP–LAP (at $\text{LQ} = 75 \text{ ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$) from baseline that was achieved in the conscious state. This allowed assessment of the pulmonary vasodilator

response to lemakalim at the same level of vasomotor tone in the conscious and sevoflurane-anesthetized states.

Protocol 2: Effect of Desflurane Anesthesia on the Pulmonary Vascular Response to Lemakalim.

We investigated the effect of desflurane anesthesia on the pulmonary vascular response to cumulative doses of lemakalim in the presence of precontraction with U46619. For each conscious dog ($n = 7$), LPQ plots were obtained in the baseline condition, during precontraction with U46619 ($0.16 \pm 0.02 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ intravenously), and during the cumulative administration of lemakalim as described in protocol 1. On a different day, this protocol was repeated in the same seven dogs during desflurane anesthesia. Anesthesia with desflurane was induced as described in protocol 1, and the end-tidal concentration was maintained at 10.1–11.5% (minimum alveolar concentration, 1.4–1.6%).⁹ Desflurane was delivered *via* a vaporizer (Tec 6; Ohmeda, Austell, GA). During desflurane anesthesia, the dose of U46619 ($0.11 \pm 0.01 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ intravenously) was titrated to achieve the same degree of precontraction induced in the conscious state.

Protocol 3: Effect of Sympathetic α_1 -Adrenoreceptor Block on the Pulmonary Vascular Response to Lemakalim in Desflurane-anesthetized Dogs.

We investigated the effect of sympathetic α_1 -adrenoreceptor inhibition on the magnitude of lemakalim pulmonary vasodilation during desflurane-induced anesthesia. This protocol tested the hypothesis that systemic hypotension during administration of lemakalim in desflurane-anesthetized dogs would result in reflex pulmonary vasoconstriction *via* sympathetic α_1 -adrenoreceptor activation,¹⁰ thereby attenuating the magnitude of lemakalim-induced pulmonary vasodilation. Sympathetic α_1 -adrenoreceptor block was achieved with the intravenous administration of prazosin (1 mg/kg). This dose abolishes the pressor response to the bolus intravenous administration of phenylephrine (5 $\mu\text{g}/\text{kg}$).¹¹ The dose–response relationship for lemakalim was obtained in six conscious and desflurane-anesthetized dogs as described in protocol 2. On a different day, this protocol was repeated in the same dogs during desflurane anesthesia after pretreatment with prazosin. Plots of LPQ were obtained at baseline, after administration of prazosin, during precontraction with U46619, and during the cumulative intravenous administration of lemakalim (0.1, 0.5, and $1.0 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$). The highest dose of lemakalim ($5.0 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) was not administered during sympa-

thetic α_1 -adrenoreceptor block because it resulted in circulatory collapse. A second dose of prazosin (0.5 mg/kg) was administered before starting the lemakalim infusion to ensure the efficacy of sympathetic α_1 -adrenoreceptor block. The doses of U46619 in the desflurane-anesthetized state ($0.12 \pm 0.01 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) and after the administration of prazosin in the desflurane-anesthetized state ($0.11 \pm 0.01 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) were titrated to achieve the same degree of precontraction induced in the conscious intact state ($0.14 \pm 0.01 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$).

Protocol 4: Effect of Indomethacin on the Pulmonary Vascular Response to Lemakalim in Conscious and Desflurane-anesthetized Dogs. We investigated the effect of cyclooxygenase inhibition with indomethacin on the magnitude of lemakalim-induced pulmonary vasodilation. Cyclooxygenase inhibition was achieved *via* the intravenous administration of indomethacin (5 mg/kg). This dose inhibits prostaglandin synthesis and abolishes the pulmonary pressor response to arachidonic acid.¹² The dose-response relationship for lemakalim was first obtained in five intact conscious dogs as described in protocol 1. On a different day, LPQ plots were obtained in the same conscious dogs at baseline, 45 min after administration of indomethacin, during precontraction with U46619, and during the cumulative intravenous administration of lemakalim. This protocol was repeated on separate days in the same dogs during desflurane anesthesia with or without pretreatment with indomethacin. Anesthesia with desflurane was induced and maintained as described in protocol 2. The doses of U46619 after the administration of indomethacin in the conscious state ($0.11 \pm 0.01 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) and in the desflurane-anesthetized state ($0.10 \pm 0.01 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) were titrated to achieve the same degree of precontraction induced in the conscious state ($0.13 \pm 0.01 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$).

Drug Preparation

All solutions were prepared on the day of the experiment. U46619 was diluted in 0.9% saline. Lemakalim and prazosin HCl (Pfizer, Groton, CT) were dissolved in 95% ethanol and then diluted in sterile water. Indomethacin (Sigma) was dissolved in sterile water with 114 g sodium carbonate.

Data Analysis

Phasic and mean vascular pressures and LQ were displayed continuously on an eight-channel strip-chart recorder (2800; Gould, Eastlake, OH). Mean pressures and

LQ, measured at end-expiration, were obtained with the use of passive electronic filters with a 2-s time constant. All vascular pressures were referenced to atmospheric pressure before and after each LPQ plot. The analog pressure and LQ signals were digitally converted and multiplexed (PCM-8; Medical Systems, Greenvale, NY) and stored on videotape (videocassette recorder AG-1260; Panasonic, Secaucus, NJ) for later playback and analysis.

The LPQ relationship was linear by inspection over the empirically measured range of LQ. Therefore, linear regression analysis was used to calculate the slope and intercept for PAP-LAP (or PAP-0 if LAP was ≤ 0 mmHg) as a function of LQ in each individual experiment. PAP-LAP intercept values were calculated at the midrange of empirically measured LQ in each protocol. This approach minimized the variance in the PAP-LAP intercept and avoided the use of intercept values outside the range of our empirical measurements; *i.e.*, PAP-LAP was not measured at $\text{LQ} = 0 \text{ ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$. The correlation coefficient for the LPQ relationship in each protocol averaged ≥ 0.98 . Multivariate analysis of variance in the form of Hotelling's T^2 was used to assess the effects of sevoflurane, desflurane, indomethacin, prazosin, U46619, and lemakalim on the regression parameters obtained in each experiment within each specific protocol.

The pulmonary vasodilator response to lemakalim ($\text{LQ} = 75 \text{ ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$) was expressed as the percentage decrease in precontraction with U46619, which was calculated with the following formula^{4,7,13}:

$$\frac{(\text{PAP-LAP})_{\text{U46619}} - (\text{PAP-LAP})_{\text{lemakalim}}}{(\text{PAP-LAP})_{\text{U46619}} - (\text{PAP-LAP})_{\text{baseline}}} \times 100$$

Thus, a lemakalim-induced decrease in PAP-LAP of 100% represents a complete reversal of U46619 precontraction and a full return to the baseline LPQ relationship. One-way analysis of variance followed by Student's *t* test for paired comparisons was used to assess the pulmonary vascular effects of lemakalim within each group. Two-way analysis of variance followed by Student's *t* test for paired comparisons was used to assess the effects of the volatile anesthetic agents on the magnitude of lemakalim-induced pulmonary vasodilation. Student's *t* test for paired comparisons was also used to assess changes in steady-state hemodynamics and blood gases. All values are presented as means \pm SE.

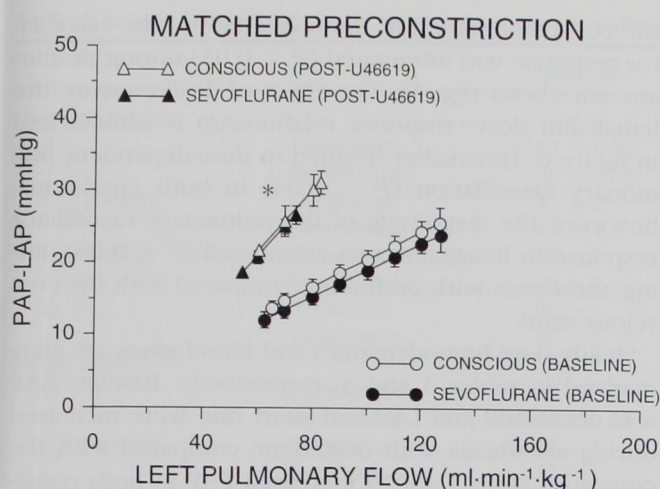


Fig. 1. Composite left pulmonary vascular pressure–flow (LPQ) plots in six dogs at baseline and after preconstriction with U46619 ($P < 0.01$) in the conscious state and during sevoflurane anesthesia. Compared with the conscious state, sevoflurane had no net effect on the baseline LPQ relationship. The dose of U46619 was titrated to achieve the same degree of preconstriction in the conscious and sevoflurane-anesthetized states.

Results

Protocol 1: Effect of Sevoflurane Anesthesia on Lemakalim-induced Pulmonary Vasodilation

Sevoflurane had no net effect on the baseline LPQ relationship compared with the conscious state (fig. 1). Compared with the baseline condition, U46619 caused pulmonary vasoconstriction ($P < 0.05$) in the conscious and sevoflurane-anesthetized states (fig. 1). A lower ($P < 0.05$) dose of U46619 was required during sevoflurane administration to match the same degree of preconstriction achieved in the conscious state. After preconstriction with U46619, lemakalim ($1.0 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) resulted in pulmonary vasodilation in the conscious state and during sevoflurane anesthesia (fig. 2). The effect of sevoflurane on the lemakalim dose–response relationship is summarized in figure 3. Lemakalim resulted in pulmonary vasodilation ($P < 0.05$) in both conditions. The magnitude of the pulmonary vasodilator response to lemakalim was not significantly altered during sevoflurane anesthesia compared with the conscious state.

Steady-state hemodynamics and blood gases are summarized in tables 1 and 2, respectively. Baseline SAP was decreased and heart rate was increased during anesthesia with sevoflurane compared with the conscious state. U46619 increased PAP in the conscious and sevoflurane-anesthetized states. Lemakalim decreased SAP and in-

creased heart rate and LQ in both conditions. Baseline blood gases were similar in conscious and sevoflurane-anesthetized dogs (table 2). U46619 decreased mixed venous pH and oxyhemoglobin saturation in both conditions. Lemakalim increased mixed venous oxygen tension and oxyhemoglobin saturation in both conditions.

Protocol 2: Effect of Desflurane Anesthesia on Lemakalim-induced Pulmonary Vasodilation

Desflurane had no net effect on the baseline LPQ relationship compared with the conscious state (fig. 4).

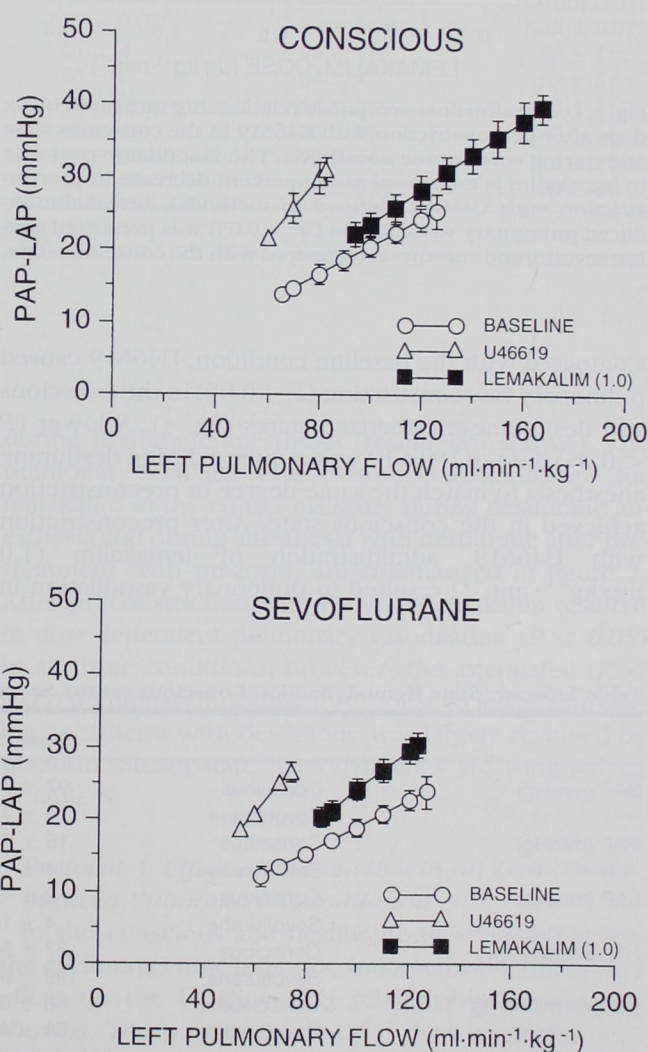


Fig. 2. Composite left pulmonary vascular pressure–flow (LPQ) plots in six dogs at baseline, after preconstriction with U46619, and during administration of lemakalim ($1.0 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ intravenously) in the conscious state (top) and during sevoflurane anesthesia (bottom). In the conscious state and during anesthesia with sevoflurane, this dose of lemakalim caused a rightward shift in the LPQ relationship, indicating pulmonary vasodilation.

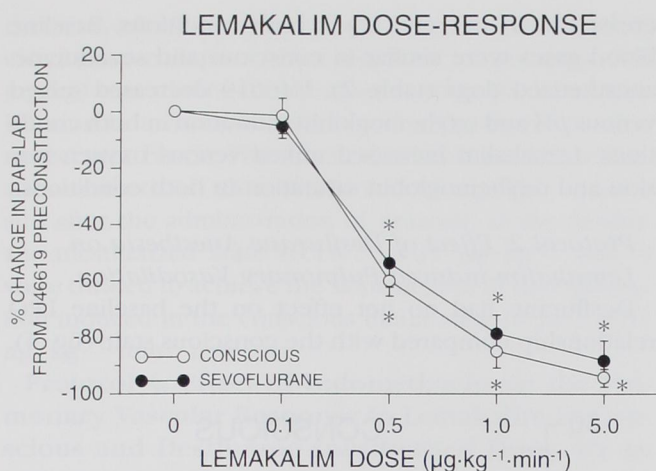


Fig. 3. Lemakalim dose-response relationship measured in six dogs after preconstriction with U46619 in the conscious state and during sevoflurane anesthesia. The vasodilator response to lemakalim is expressed as the percent decrease in preconstriction with U46619 (defined in methods). Lemakalim-induced pulmonary vasodilation ($P < 0.05$) was preserved during sevoflurane anesthesia compared with the conscious state.

Compared with the baseline condition, U46619 caused pulmonary vasoconstriction ($P < 0.05$) in the conscious and desflurane-anesthetized states (fig. 4). A lower ($P < 0.05$) dose of U46619 was required during desflurane anesthesia to match the same degree of preconstriction achieved in the conscious state. After preconstriction with U46619, administration of lemakalim ($1.0 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) resulted in pulmonary vasodilation in

the conscious state, but the magnitude of the vasodilator response was attenuated ($P < 0.05$) during desflurane anesthesia (fig. 5). The effect of desflurane on the lemakalim dose-response relationship is summarized in figure 6. Lemakalim resulted in dose-dependent pulmonary vasodilation ($P < 0.05$) in both conditions; however, the magnitude of the pulmonary vasodilator response to lemakalim was attenuated ($P < 0.05$) during anesthesia with desflurane compared with the conscious state.

Steady-state hemodynamics and blood gases are summarized in tables 3 and 4, respectively. Baseline SAP was decreased and LAP and heart rate were increased during anesthesia with desflurane compared with the conscious state. U46619 increased PAP in both conditions. Lemakalim decreased SAP and LAP and increased heart rate in both conditions. Lemakalim increased LQ in the conscious state, whereas LQ was unchanged during desflurane anesthesia. Baseline blood gases were similar in conscious and desflurane-anesthetized dogs (table 4). U46619 decreased systemic arterial and mixed venous pH and oxyhemoglobin saturation in both conditions. Lemakalim decreased mixed venous carbon dioxide tension and increased mixed venous oxygen tension and oxyhemoglobin saturation in both conditions.

Protocol 3: Effect of Sympathetic α_1 -adrenoreceptor Block on Lemakalim Pulmonary Vasodilation

The sympathetic α_1 -adrenoreceptor antagonist, prazosin, had no net effect on the baseline LPQ relationship

Table 1. Steady State Hemodynamics: Conscious versus Sevoflurane

		Baseline	U46619	Lem 1.0	Lem 5.0
SAP (mmHg)	Conscious	97 ± 4	108 ± 4	91 ± 3†	57 ± 4†
	Sevoflurane	76 ± 2‡	88 ± 3‡	69 ± 3†‡	42 ± 2†‡
PAP (mmHg)	Conscious	16 ± 1	26 ± 1*	26 ± 1	21 ± 2
	Sevoflurane	14 ± 1	25 ± 1*	23 ± 1	17 ± 1†
LAP (mmHg)	Conscious	2 ± 1	4 ± 1	1 ± 1†	2 ± 1†
	Sevoflurane	4 ± 1	5 ± 1	5 ± 1‡	6 ± 1
HR (beats/min)	Conscious	97 ± 5	94 ± 4	152 ± 9†	157 ± 14†
	Sevoflurane	129 ± 8‡	130 ± 6‡	141 ± 6†	144 ± 8†
LQ (ml · min ⁻¹ · kg ⁻¹)	Conscious	66 ± 6	60 ± 5	94 ± 8†	89 ± 7†
	Sevoflurane	51 ± 4	55 ± 2	86 ± 6†	59 ± 8

SAP = mean systemic arterial pressure; PAP = mean pulmonary arterial pressure; LAP = mean left atrial pressure; HR = heart rate; LQ = mean left pulmonary blood flow.

Values are mean ± SEM. Lemakalim (Lem) data for doses of 1 and 5 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$.

* $P < 0.05$ U46619 versus baseline.

† $P < 0.05$ lemakalim versus U46619.

‡ $P < 0.05$ sevoflurane versus conscious.

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Table 2. Steady State Blood Gases: Conscious versus Sevoflurane

		Baseline	U46619	Lem 1.0	Lem 5.0
Systemic arterial	pH				
	Conscious	7.41 ± 0.02	7.37 ± 0.01*	7.40 ± 0.01†	7.39 ± 0.01
	Sevoflurane	7.39 ± 0.02	7.35 ± 0.02	7.34 ± 0.02‡	7.34 ± 0.02
	P _{CO₂} (mmHg)				
	Conscious	41 ± 2	41 ± 2	38 ± 1†	38 ± 2†
	Sevoflurane	41 ± 1	45 ± 2*	43 ± 2	41 ± 2
P _{O₂} (mmHg)	Conscious	95 ± 2	84 ± 3*	88 ± 2	86 ± 3
	Sevoflurane	93 ± 2	84 ± 3	84 ± 6	77 ± 2†
	S _{O₂} (%)				
	Conscious	97 ± 1	94 ± 1*	95 ± 1	94 ± 1
Mixed venous	pH				
	Conscious	7.38 ± 0.01	7.33 ± 0.01*	7.37 ± 0.01†	7.37 ± 0.01†
	Sevoflurane	7.36 ± 0.02	7.32 ± 0.02*	7.31 ± 0.02‡	7.32 ± 0.02‡
	P _{CO₂} (mmHg)				
	Conscious	48 ± 1	51 ± 2	45 ± 1†	42 ± 1†
	Sevoflurane	47 ± 1	55 ± 2*	54 ± 4‡	52 ± 3‡
P _{O₂} (mmHg)	Conscious	42 ± 1	40 ± 2*	54 ± 2†	53 ± 2†
	Sevoflurane	42 ± 2	40 ± 4	46 ± 2†	48 ± 3†
	S _{O₂} (%)				
	Conscious	67 ± 1	57 ± 2*	79 ± 1†	78 ± 2†
	Sevoflurane	67 ± 2	57 ± 5*	67 ± 2†‡	64 ± 5‡

P_{CO₂} = carbon dioxide tension; P_{O₂} = oxygen tension; S_{O₂} = oxyhemoglobin saturation.

Values are mean ± SEM.

* $P < 0.05$ U46619 versus baseline.

† $P < 0.05$ lemakalim versus U46619.

‡ $P < 0.05$ sevoflurane versus conscious.

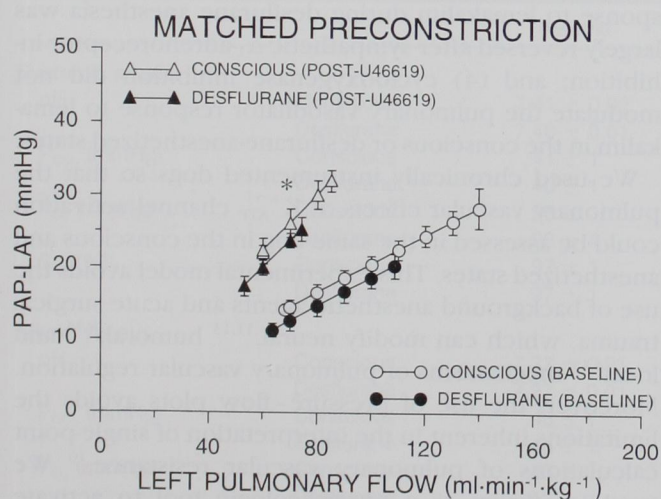


Fig. 4. Composite left pulmonary vascular pressure–flow (LPQ) plots in seven dogs at baseline and after preconstriction with U46619 ($P < 0.01$) in the conscious state and during desflurane anesthesia. Compared with the conscious state, desflurane had no net effect on the baseline LPQ relationship. The dose of U46619 was titrated to achieve the same degree of preconstriction in the conscious and desflurane-anesthetized states.

during desflurane anesthesia (results not shown). The pulmonary vascular dose–response relationships for lemakalim in the conscious state, during desflurane anesthesia and during anesthesia with desflurane after pretreatment with prazosin, are summarized in figure 7. After preconstriction with U46619, lemakalim resulted in dose-dependent pulmonary vasodilation ($P < 0.05$) in all three conditions; however, the attenuated ($P < 0.05$) pulmonary vasodilator response to lemakalim during anesthesia with desflurane was largely reversed by prazosin. Steady-state hemodynamics are summarized in table 5.

Protocol 4: Effect of Indomethacin on Lemakalim-induced Pulmonary Vasodilation

In the conscious and desflurane-anesthetized states, the cyclooxygenase inhibitor, indomethacin, had no net effect on the baseline LPQ relationship (results not shown). The pulmonary vascular dose–response relationships for lemakalim in the conscious and desflurane-anesthetized states with or without pretreatment with indomethacin are summarized in figure 8. After preconstriction with U46619, lemakalim resulted in dose-dependent pulmonary vasodilation ($P < 0.05$) in all four conditions. Indomethacin did not alter the magnitude

of the pulmonary vasodilator response to lemakalim in the conscious state. The attenuated pulmonary vasodilator response to lemakalim during desflurane anesthesia was still apparent after pretreatment with indomethacin. Steady-state hemodynamics are summarized in table 6.

Discussion

This study demonstrated that (1) sevoflurane and desflurane anesthesia had no net effect on the baseline LPQ

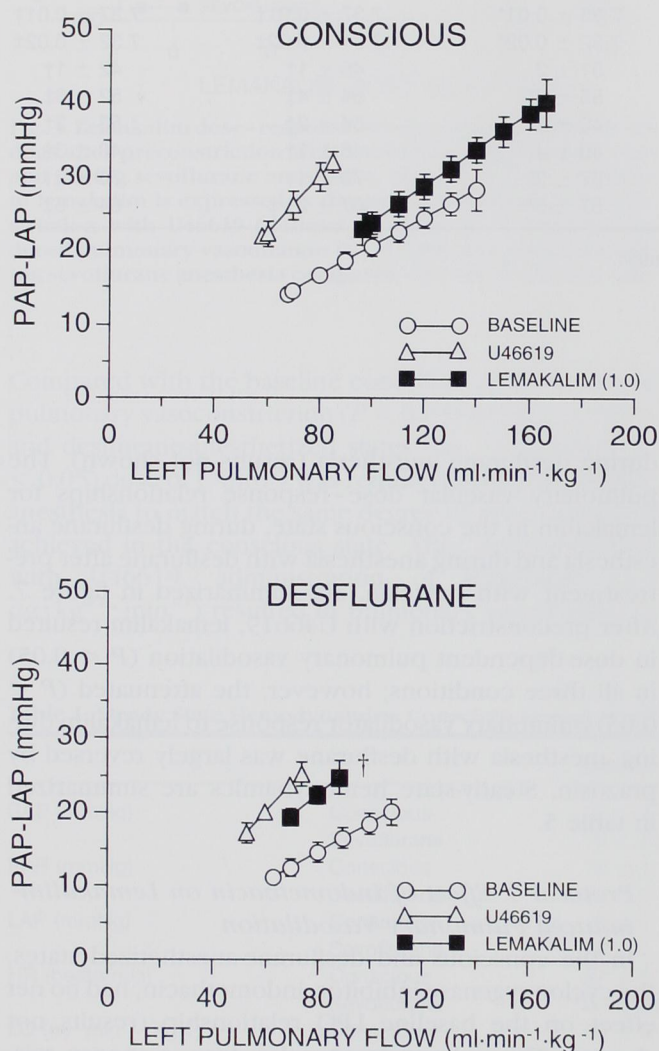


Fig. 5. Composite left pulmonary vascular pressure-flow (LPQ) plots in seven dogs at baseline, after precontraction with U46619, and during administration of lemakalim ($1.0 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ intravenously) in the conscious state (top) and during desflurane anesthesia (bottom). This dose of lemakalim caused pulmonary vasodilation, but the magnitude of the vasodilator response was attenuated ($\dagger P < 0.05$) during desflurane anesthesia.

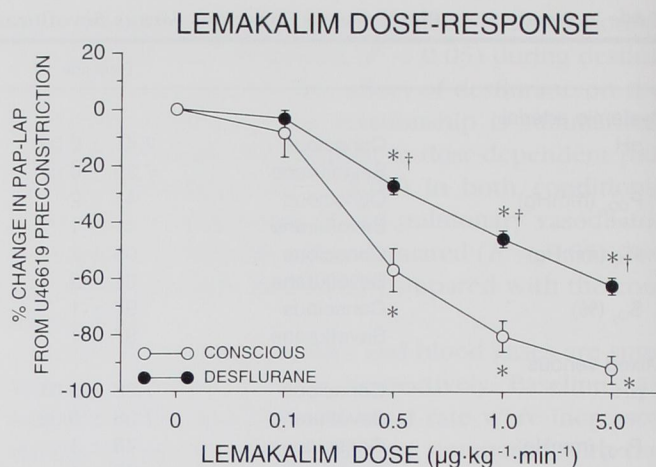


Fig. 6. Lemakalim dose-response relationship measured in seven dogs after precontraction with U46619 in the conscious state and during desflurane anesthesia. The vasodilator response to lemakalim is expressed as the percent decrease in precontraction with U46619 (defined in methods). Lemakalim-induced pulmonary vasodilation ($*P < 0.05$) was attenuated ($\dagger P < 0.05$) during desflurane anesthesia compared with the conscious state.

relationship; (2) the pulmonary vasodilator response to the K^+_{ATP} channel agonist, lemakalim, was not altered during sevoflurane anesthesia but was attenuated during desflurane anesthesia compared with the conscious state; (3) the attenuated pulmonary vasodilator response to lemakalim during desflurane anesthesia was largely reversed after sympathetic α_1 -adrenoreceptor inhibition; and (4) cyclooxygenase inhibition did not modulate the pulmonary vasodilator response to lemakalim in the conscious or desflurane-anesthetized states.

We used chronically instrumented dogs so that the pulmonary vascular effects of K^+_{ATP} channel activation could be assessed in the same dog in the conscious and anesthetized states. This experimental model avoids the use of background anesthetic agents and acute surgical trauma, which can modify neural,^{11,13} humoral,^{8,14} and local^{4,15} mechanisms of pulmonary vascular regulation. Moreover, the use of pressure-flow plots avoids the limitations inherent in the interpretation of single-point calculations of pulmonary vascular resistance.¹⁶ We used lemakalim as a pharmacologic tool to activate K^+_{ATP} -mediated pulmonary vasodilation.³ This is based on previous observations that lemakalim is a potent and selective activator of K^+_{ATP} channels in the pulmonary vasculature.^{2,4}

Sevoflurane and desflurane have been reported to cause systemic vasodilation.^{17,18} In contrast, neither an-

VOLATILE ANESTHETICS AND K^+_{ATP} PULMONARY VASODILATIONTable 3. Steady State Hemodynamics: Conscious *versus* Desflurane

		Baseline	U46619	Lem 1.0	Lem 5.0
SAP (mmHg)	Conscious	98 ± 4	106 ± 4	89 ± 3†	56 ± 3†
	Desflurane	72 ± 6‡	88 ± 4‡	66 ± 4†‡	49 ± 2†
PAP (mmHg)	Conscious	16 ± 1	26 ± 1*	26 ± 2	21 ± 2
	Desflurane	18 ± 1	26 ± 1*	26 ± 1	22 ± 1
LAP (mmHg)	Conscious	2 ± 1	4 ± 1	1 ± 1†	2 ± 1†
	Desflurane	7 ± 1‡	9 ± 1*‡	6 ± 1†‡	7 ± 1†‡
HR (beats/min)	Conscious	105 ± 6	93 ± 5	149 ± 9†	157 ± 14†
	Desflurane	135 ± 6‡	137 ± 6‡	148 ± 5†	154 ± 5†
LQ (ml · min ⁻¹ · kg ⁻¹)	Conscious	67 ± 6	61 ± 5	97 ± 8†	89 ± 7†
	Desflurane	64 ± 5	57 ± 4	75 ± 8	65 ± 11

Values are mean ± SEM.

* $P < 0.05$ U46619 *versus* baseline.† $P < 0.05$ lemakalim *versus* U46619.‡ $P < 0.05$ desflurane *versus* conscious.

esthetic agent had a net effect on the baseline LPQ relationship compared with the conscious state. Because the normal pulmonary circulation has very little vasomotor tone, an anesthesia-induced vasodilator influence on the LPQ relationship during baseline conditions would not be expected. In contrast, volatile anesthetic agents are known to inhibit endothelium-depen-

dent vasodilation,^{15,19} which could result in a net pulmonary vasoconstrictor influence. We have reported, however, that neither nitric oxide synthase inhibition nor cyclooxygenase inhibition have a net effect on the baseline LPQ relationship in conscious dogs.^{7,12} Therefore, it was not surprising that sevoflurane and desflurane had no effect on the baseline LPQ relation-

Table 4. Steady State Blood Gases: Conscious *versus* Desflurane

		Baseline	U46619	Lem 1.0	Lem 5.0
Systemic arterial					
pH	Conscious	7.41 ± 0.02	7.38 ± 0.01*	7.40 ± 0.01†	7.39 ± 0.01
	Desflurane	7.40 ± 0.01	7.36 ± 0.01*	7.36 ± 0.01‡	7.35 ± 0.02‡
P _{CO₂} (mmHg)	Conscious	41 ± 1	40 ± 1	38 ± 1†	37 ± 2†
	Desflurane	40 ± 1	44 ± 2*	43 ± 2‡	42 ± 2
P _{O₂} (mmHg)	Conscious	96 ± 2	84 ± 4*	89 ± 3	84 ± 3
	Desflurane	93 ± 4	86 ± 6	84 ± 3	81 ± 4
S _{O₂} (%)	Conscious	97 ± 1	94 ± 1*	96 ± 1†	94 ± 1
	Desflurane	97 ± 1	94 ± 1*	93 ± 2	90 ± 2
Mixed venous					
pH	Conscious	7.37 ± 0.01	7.33 ± 0.01*	7.37 ± 0.01†	7.37 ± 0.01†
	Desflurane	7.37 ± 0.01	7.32 ± 0.01*	7.34 ± 0.01‡	7.32 ± 0.01‡
P _{CO₂} (mmHg)	Conscious	48 ± 1	50 ± 2	44 ± 1†	42 ± 1†
	Desflurane	45 ± 1	51 ± 2*	48 ± 2†	47 ± 2†
P _{O₂} (mmHg)	Conscious	43 ± 1	39 ± 2*	50 ± 4†	51 ± 3†
	Desflurane	42 ± 1	42 ± 2	51 ± 2†	48 ± 3†
S _{O₂} (%)	Conscious	67 ± 1	57 ± 1*	76 ± 4†	77 ± 2†
	Desflurane	69 ± 1	62 ± 2*	74 ± 2†	69 ± 3†‡

Values are mean ± SEM.

* $P < 0.05$ U46619 *versus* baseline.† $P < 0.05$ lemakalim *versus* U46619.‡ $P < 0.05$ desflurane *versus* conscious.

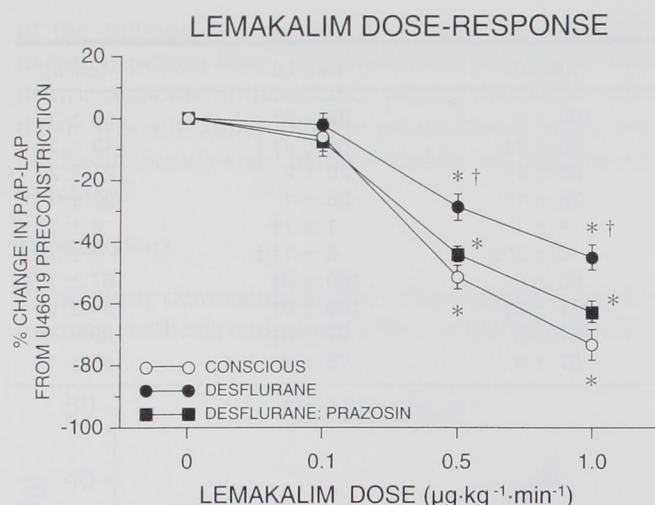


Fig. 7. Lemakalim dose-response relationship measured in six dogs after preconstriction with U46619 in the conscious state and during desflurane anesthesia. Vasodilator response to lemakalim is expressed as the percent decrease in preconstriction with U46619 (defined in methods). The attenuated ($\dagger P < 0.05$) lemakalim-induced pulmonary vasodilation ($*P < 0.05$) during desflurane anesthesia was largely reversed after pretreatment with prazosin.

ship in the current study. We should note, however, that sevoflurane and desflurane reduced the concentration of U46619 required to achieve the same degree of preconstriction observed in the conscious state. This

could be due to an inhibitory effect of both anesthetic agents on the endothelial production of nitric oxide. In contrast to baseline conditions, preconstriction with U46619 stimulates the endogenous production of nitric oxide, as manifested by a leftward shift in the pulmonary vascular dose-response relationship for U46619 after nitric oxide synthase inhibition.⁷

Recently, interactions between volatile anesthetic agents and K^+_{ATP} channels in various tissues have been described.²⁰⁻²⁵ Several studies have demonstrated that activation of K^+_{ATP} channels plays an important role in coronary vasodilation induced by volatile anesthetic agents.²⁰⁻²² In contrast, we have demonstrated previously that halothane and enflurane attenuate lemakalim-induced pulmonary vasodilation in chronically instrumented dogs.⁴ In *in vitro* studies, we also observed that halothane and isoflurane attenuated the endothelium-dependent pulmonary vasorelaxant responses to K^+_{ATP} channel activation.^{26,27} In the current study, desflurane, but not sevoflurane, attenuated lemakalim-induced pulmonary vasodilation. To our knowledge, this is the first study to investigate the effects of sevoflurane and desflurane anesthesia on K^+_{ATP} channel activity. Only one study has reported that desflurane inhibits a potassium channel current in human neuronal cells at clinically relevant concentrations.²⁸

The possible mechanisms by which desflurane attenuated K^+_{ATP} channel-mediated pulmonary vasodilation

Table 5. Steady State Hemodynamics: Effect of Prazosin

		Baseline	U46619	Lem 1.0
SAP (mmHg)	Conscious	93 ± 5	103 ± 4	89 ± 2†
	Desflurane	72 ± 7‡	93 ± 5‡	69 ± 7†‡
	Des + Praz	61 ± 4‡	78 ± 3‡	47 ± 3†‡
PAP (mmHg)	Conscious	15 ± 2	24 ± 2*	27 ± 2
	Desflurane	18 ± 1	26 ± 1*	25 ± 1
	Des + Praz	18 ± 1	27 ± 1*	24 ± 1
LAP (mmHg)	Conscious	2 ± 1	3 ± 1	1 ± 1†
	Desflurane	6 ± 1	8 ± 1	5 ± 1†
	Des + Praz	4 ± 1	5 ± 1	3 ± 1
HR (beats/min)	Conscious	97 ± 6	93 ± 5	150 ± 10†
	Desflurane	137 ± 11‡	140 ± 6‡	150 ± 5†
	Des + Praz	142 ± 8‡	145 ± 5‡	151 ± 8
LQ (ml · min ⁻¹ · kg ⁻¹)	Conscious	65 ± 8	56 ± 3	89 ± 8†
	Desflurane	64 ± 6	56 ± 4	78 ± 7†
	Des + Praz	59 ± 4	57 ± 7	78 ± 5†

Values are mean ± SEM.

* $P < 0.05$ U46619 versus baseline.

† $P < 0.05$ lemakalim versus U46619.

‡ $P < 0.05$ desflurane (Des) or Des + prazosin (Praz) versus conscious.

LEMAKALIM DOSE-RESPONSE

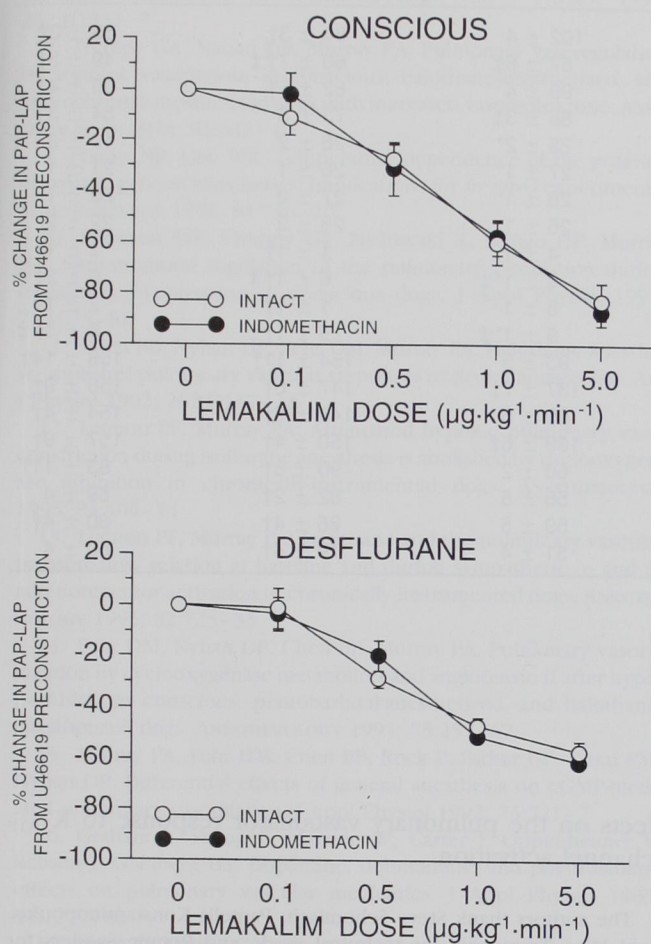


Fig. 8. Lemakalim dose-response relationship measured in five dogs after preconstriction with U46619 with or without pretreatment with indomethacin in the conscious state (top) and during desflurane anesthesia (bottom). Vasodilator response to lemakalim is expressed as the percent decrease in preconstriction with U46619 (defined in Methods). Indomethacin did not alter the magnitude of the pulmonary vasodilator response to lemakalim in the conscious or desflurane-anesthetized states.

could involve (1) activation of reflex vasoconstrictor mechanisms, (2) inhibition of endothelium-dependent vasodilator mechanisms, or (3) a direct effect of desflurane on vascular smooth muscle K^+_{ATP} channels. Administration of lemakalim resulted in systemic hypotension in the conscious state, and this effect was even more pronounced during anesthesia with desflurane. Systemic hypotension causes reflex pulmonary vasoconstriction mediated by sympathetic α_1 -adrenoreceptor activation in conscious dogs.¹⁰ We have reported

previously that combined neurohumoral block had no effect on the magnitude of lemakalim-induced pulmonary vasodilation in the conscious or halothane-anesthetized state.⁴ In this study, however, sympathetic α_1 -adrenoreceptor inhibition with prazosin reversed the attenuation of lemakalim-induced pulmonary vasodilation during desflurane anesthesia. These results suggest that reflex pulmonary vasoconstriction mediated by sympathetic α_1 -adrenoreceptors acted to offset the pulmonary vasodilator response to lemakalim during desflurane anesthesia. This is consistent with our previous observation that phenylephrine-induced pulmonary vasoconstriction is potentiated during anesthesia with desflurane compared with the conscious state.²⁹ Thus, the inhibitory effect of desflurane on K^+_{ATP} channel-mediated pulmonary vasodilation appears to be at least partly a secondary effect caused by activation of sympathetic α_1 -adrenoreceptors.

Recent evidence indicates that K^+_{ATP} channels are expressed in both vascular smooth muscle and endothelial cells.³⁰⁻³² Activation of endothelial K^+_{ATP} channels increases Ca^{2+} influx, which stimulates the production of endothelium-derived relaxant factors. In *in vitro* studies, we recently demonstrated that the pulmonary vasorelaxant response to lemakalim involves both an endothelium-dependent and vascular smooth muscle component.²⁶ The endothelium-dependent component of lemakalim-induced pulmonary vasorelaxation was mediated by cyclooxygenase metabolites and not by nitric oxide.²⁶ Moreover, halothane attenuated lemakalim-induced pulmonary vasorelaxation *via* an inhibitory effect on the endothelium-dependent, cyclooxygenase-mediated component of the response.²⁶ In the current *in vivo* study, we tested the hypothesis that desflurane inhibited lemakalim-induced pulmonary vasodilation *via* a similar mechanism. The attenuated response to lemakalim during desflurane anesthesia, however, was still apparent after cyclooxygenase inhibition, which suggests that this mechanism is not involved.

The possibility that desflurane directly interferes with K^+_{ATP} channels cannot be discounted. It has been suggested that inhalational anesthetic agents bind specifically to ion channels and alter their function directly.^{33,34} Inhalational anesthetic agents may alter membrane fluidity and lateral membrane pressure, which could inhibit the opening or accelerate the closing of ion channels. Additional studies are required to identify the molecular mechanisms by

Table 6. Steady State Hemodynamics: Effect of Indomethacin

		Baseline	U46619	Lem 1.0	Lem 5.0
SAP (mmHg)	Conscious	95 ± 4	102 ± 4	84 ± 3†	55 ± 3†
	Desflurane	75 ± 5‡	87 ± 6‡	66 ± 7†‡	49 ± 3†
	Con + Indo	90 ± 5	99 ± 4	82 ± 5†	55 ± 4†
	Des + Indo	72 ± 1‡	85 ± 3‡	73 ± 3	54 ± 3†
PAP (mmHg)	Conscious	15 ± 1	25 ± 2*	26 ± 2	19 ± 2
	Desflurane	18 ± 1	27 ± 1*	26 ± 1	21 ± 1
	Con + Indo	16 ± 1	26 ± 1*	27 ± 2	20 ± 1
	Des + Indo	18 ± 1	26 ± 1*	28 ± 2	22 ± 2
LAP (mmHg)	Conscious	2 ± 1	4 ± 1	1 ± 1†	2 ± 1†
	Desflurane	7 ± 1‡	9 ± 1*‡	6 ± 1†‡	6 ± 2†‡
	Con + Indo	3 ± 1	5 ± 1	1 ± 1†	2 ± 1†
	Des + Indo	7 ± 1‡	9 ± 1*‡	6 ± 1†‡	6 ± 1†‡
HR (beats/min)	Conscious	102 ± 3	93 ± 5	154 ± 11†	158 ± 14†
	Desflurane	133 ± 10‡	137 ± 7‡	147 ± 6†	156 ± 9†
	Con + Indo	95 ± 4	90 ± 5	149 ± 7†	154 ± 4†
	Des + Indo	133 ± 9‡	139 ± 6‡	150 ± 4†	157 ± 9†
LQ (ml · min ⁻¹ · kg ⁻¹)	Conscious	68 ± 3	60 ± 2	90 ± 6†	83 ± 11†
	Desflurane	61 ± 5	56 ± 5	82 ± 2†	69 ± 4
	Con + Indo	63 ± 4	59 ± 5	86 ± 4†	80 ± 4†
	Des + Indo	55 ± 7	51 ± 4	79 ± 4†	60 ± 4

Values are mean ± SEM.

* $P < 0.05$ U46619 versus baseline.

† $P < 0.05$ lemcalim versus U46619.

‡ $P < 0.05$ desflurane versus conscious.

§ $P < 0.05$ Des + indomethacin (Indo) versus conscious (Con) + Indo.

which inhalational anesthetic agents directly alter K^+_{ATP} channel activity.

In contrast to desflurane, sevoflurane had no effect on lemcalim-induced pulmonary vasodilation. These differential results may partially reflect the different effects of sevoflurane and desflurane on sympathetic α_1 -adrenoreceptors. We previously reported that, in contrast to desflurane, sevoflurane had no effect on phenylephrine-induced pulmonary vasoconstriction compared with the response measured in the conscious state.²⁹ Therefore, although the same degree of systemic hypotension was observed during anesthesia with sevoflurane and desflurane, reflex pulmonary vasoconstriction *via* sympathetic α_1 -adrenoreceptor activation did not inhibit lemcalim-induced pulmonary vasodilation during sevoflurane anesthesia.

In summary, K^+_{ATP} channel-mediated pulmonary vasodilation is preserved during sevoflurane anesthesia but is attenuated during desflurane anesthesia. This effect of desflurane does not involve the cyclooxygenase pathway but is largely mediated by reflex sympathetic α_1 -adrenoreceptor vasoconstriction. These results indicate that volatile anesthetic agents can have differential ef-

fects on the pulmonary vasodilator response to K^+_{ATP} channel activation.

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